PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION** see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
FC 874/5		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/EP 00/06540	10/07/2000	20/07/1999
Applicant		
PHARMACIA AND UPJOHN S.P.A.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 3 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

[ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

[ ] contained in the international application in written form.

[ ] filed together with the international application in computer readable form.

[ ] furnished subsequently to this Authority in written form.

[ ] furnished subsequently to this Authority in computer readble form.

[ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

[ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [ ] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

[ ] the text is approved as submitted by the applicant.

[X] the text has been established by this Authority to read as follows:

COMBINED PREPARATIONS COMPRISING DAUNORUBICIN DERIVATIVES AND HER2 ANTOBODIES

5. With regard to the **abstract,**

[X] the text is approved as submitted by the applicant.

[ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. 1

[X] as suggested by the applicant.

[ ] None of the figures.

[ ] because the applicant failed to suggest a figure.

[ ] because this figure better characterizes the invention.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 00/06540

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/70 A61K39/395 A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, MEDLINE, BIOSIS, CHEM ABS Data, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	BASELGA J ET AL: "HER2 Overexpression and Paclitaxel sensitivity in breast cancer: Therapeutic implications" ONCOLOGY,CH,S. KARGER AG, BASEL, vol. 11, no. 3, SUPPL. 02, March 1997 (1997-03), pages 43-48, XP002100077 ISSN: 0030-2414 abstract page 46, column 2, paragraph 4 -page 47, column 1 ---	1-14
Y	US 5 677 171 A (SHEPARD H MICHAEL ET AL) 14 October 1997 (1997-10-14) claims 18,19,37,39 --- -/--	1-14

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
20 December 2000	29/12/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040 Tx. 31 651 epo nl Fax (+31-70) 340-3016	Gonzalez Ramon, N

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 00/06540

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5 705 157 A (GREENE MARK I) 6 January 1998 (1998-01-06) claims 2,5	1-14
E	WO 00 69460 A (GENENTECH INC) 23 November 2000 (2000-11-23) abstract page 11, line 20-23; claims 2,3,7	1-14
X	WO 99 31140 A (GENENTECH INC) 24 June 1999 (1999-06-24) page 12, line 4-6; claims 1,4 abstract	1-14
E	WO 00 44225 A (DANNENBERG ANDREW J ;CORNELL RES FOUNDATION INC (US); SUBBARAMAIAH) 3 August 2000 (2000-08-03) page 21 -page 22; claims 2,3,5	1-14
E	WO 00 61185 A (BELLET ROBERT E ;VOGEL CHARLES L (US)) 19 October 2000 (2000-10-19) claims 1,3	1-14
Y	WO 89 06692 A (GENENTECH INC) 27 July 1989 (1989-07-27) page 11, line 12-25; claims 23,28,32 page 12, line 33-35	1-14
Y	EP 0 328 147 A (BRISTOL MYERS CO) 16 August 1989 (1989-08-16) page 8 -page 9; claims 5,11-13,24,26	1-14

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 00/06540

Patent document cited in search report		Publication date	Patent family member(s)			Publication date
US 5677171	A	14-10-1997	US	5772997	A	30-06-1998
			US	5770195	A	23-06-1998
			US	5720954	A	24-02-1998
			JP	11335297	A	07-12-1999
			JP	11255666	A	21-09-1999
			JP	3502885	T	04-07-1991
			WO	8906692	A	27-07-1989
			US	5720937	A	24-02-1998
			US	5725856	A	10-03-1998
US 5705157	A	06-01-1998	NONE			
WO 0069460	A	23-11-2000	NONE			
WO 9931140	A	24-06-1999	AU	1908199	A	05-07-1999
			EP	1037926	A	27-09-2000
			NO	20002957	A	11-08-2000
WO 0044225	A	03-08-2000	NONE			
WO 0061185	A	19-10-2000	NONE			
WO 8906692	A	27-07-1989	JP	11335297	A	07-12-1999
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			US	5770195	A	23-06-1998
			US	5720954	A	24-02-1998
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			IE	64650	B	23-08-1995
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			IL	106992	A	24-06-1994
			JP	1246295	A	02-10-1989
			JP	2740841	B	15-04-1998
			KR	9615398	B	13-11-1996
			NO	178229	B	06-11-1995
			NO	950099	A	14-08-1989
			NZ	227911	A	27-11-1990
			PT	89683	A,B	04-10-1989
			US	5122368	A	16-06-1992
			ZA	8900938	A	29-11-1989

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(30) Priority Data:
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(71) Applicant *(for all designated States except US)*: **PHARMACIA & UPJOHN S.P.A.** [IT/IT]; Via Robert Koch, 1.2, I-20152 Milano (IT).

(72) Inventors; and

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(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
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(88) Date of publication of the international search report:
17 May 2001

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 01/05425 A3

(54) Title: COMBINED PREPARATIONS COMPRISING DAUNORUBICIN DERIVATIVES AND HER2 ANTIBODIES

(57) Abstract: There are provided the combined use of 4-demethoxy-3'-deamino-3'-aziridinyl-4'-methansulfonyl daunorubicin or 4-demethoxy-N,N-bis(2-chloroethyl)-4'-methansulfonyl daunorubicin and a recombinant humanized anti-HER2 antibody, preferably trastuzumab, in the treatment of tumors and the use of said combination in the treatment and/or prevention of tumor metastasis.

INTERNATIONAL SEARCH REPORT

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PCT/EP 00/06540

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Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Gonzalez Ramon, N

Form PCT/ISA/210 (second sheet) (July 1992)

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INTERNATIONAL SEARCH REPORT

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Interr. ıal Application No
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		JP 3502885 T	04-07-1991
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		US 5720937 A	24-02-1998
		US 5725856 A	10-03-1998
US 5705157 A	06-01-1998	NONE	
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		EP 1037926 A	27-09-2000
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		JP 3502885 T	04-07-1991
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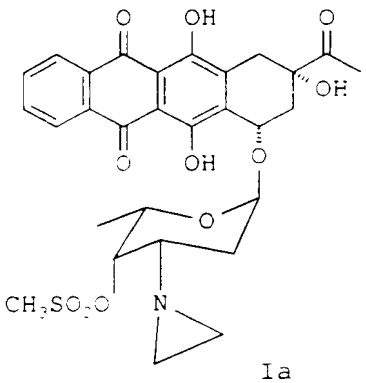
		NZ 227911 A	27-11-1990
		PT 89683 A,B	04-10-1989
		US 5122368 A	16-06-1992
		ZA 8900938 A	29-11-1989

Title: "Combined preparations comprising antitumor agents"

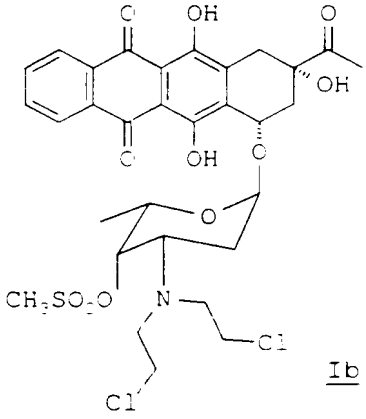
The present invention pertains to the field of neoplastic disease therapy. Particularly, this invention provides an antitumor composition comprising an alkylating anthracycline and a recombinant humanized anti-HER2 antibody, for example the recombinant humanized monoclonal antibody (rhuMab) anti-HER2, trastuzumab (Herceptin™), having a synergistic or additive antineoplastic effect.

The present invention provides, in a first aspect, a pharmaceutical composition for use in antineoplastic therapy in mammals, including humans, comprising

- an alkylating anthracycline of formula Ia or Ib



Ia



Ib

- a recombinant humanized anti-HER2 antibody and a pharmaceutically acceptable carrier or excipient.

The recombinant humanized anti-HER2 antibody is preferably, the recombinant humanized monoclonal antibody anti-HER2 trastuzumab.

The chemical names of the alkylating anthracyclines of formula Ia and Ib are 4-demethoxy-3'-deamino-3'-aziridinyl-4'-methansulfonyl daunorubicin (Ia) and 4-demethoxy-N,N-bis(2-chloroethyl)-4'-methansulfonyl daunorubicin (Ib). These alkylating anthracyclines were described in Anticancer Drug Design (1995), vol. 10, 641-653, and claimed respectively in US-A-5,532,219 and US-A-5,496,800. Both compounds intercalate

into DNA via the chromophore and alkylate guanine at N position in DNA minor groove via their reactive moiety on position 3' of the amino sugar. Compounds Ia and Ib are able to circumvent the resistance to all major classes of cytotoxics, indicating that the compounds represent a new class of cytotoxic antitumor drugs.

The recombinant humanized monoclonal antibody anti-HER2 trastuzumab (Herceptin™) is described in various scientific publications, for example Cancer Res., 1998, 58:2825-2831.

The present invention also provides a product comprising an alkylating anthracycline of formula Ia or Ib as defined above and a recombinant humanized anti-HER2 antibody, preferably the recombinant humanized monoclonal antibody anti-HER2 trastuzumab, as combined preparation for simultaneous, separate or sequential use in antitumor therapy.

A further aspect of the present invention is to provide a method of treating a mammal, including a human, suffering from a neoplastic disease comprising administering to said mammal an alkylating anthracycline of formula Ia or Ib as defined above and a recombinant humanized anti-HER2 antibody, preferably the recombinant humanized monoclonal antibody anti-HER2 trastuzumab, in amounts effective to produce a synergistic antineoplastic effect.

A still further aspect of the present invention is to provide a method for lowering the side effects caused by antineoplastic therapy with an antineoplastic agent in a mammal, including a human, in need thereof, the method comprising administering to said mammal a combined preparation comprising an alkylating anthracycline of formula Ia or Ib as defined above, and a recombinant humanized anti-HER2 antibody, preferably the the recombinant humanized monoclonal antibody anti-HER2 trastuzumab, in amounts effective to produce a synergistic antineoplastic effect.

By the term "a synergistic antineoplastic effect" as used herein is meant the inhibition of the growth tumor, preferably

the complete regression of the tumor, administering an effective amount of the combination of an alkylating anthracycline of formula Ia or Ib as defined above and a recombinant humanized anti-HER2 antibody to mammals, including humans.

By the term "administered" or "administering" as used herein is meant any acceptable manner of administering a drug to a patient which is medically acceptable including parenteral and oral administration. By "parenteral" is meant intravenous, subcutaneous and intramuscular administration. Oral administration includes administering the costituents of the combined preparation in a suitable oral form such as, e.g., tablets, capsules, suspensions, solutions, emulsions, powders, syrups and the like. Parenteral administration includes administering the costituents of the combined preparation by subcutaneous, intravenous or intramuscular injections.

The actual preferred method and order of administration of the combined preparations of the invention may vary according to, inter alia, the particular pharmaceutical formulation of the alkylating anthracycline of formula Ia or Ib as defined above being utilized, the particular pharmaceutical formulation of the recombinant humanized anti-HER2 antibody being utilized, the particular cancer being treated, and the particular patient being treated.

The dosage ranges for the administration of the combined preparation may vary with the age, condition, sex and extent of the disease in the patient and can be determined by one of skill in the art.

The dosage regimen must therefore be tailored to the particular of the patient's conditions, response and associate treatments in a manner which is conventional for any therapy, and may need to be adjusted in response to changes in conditions and/or in light of other clinical conditions.

In the method of the subject invention, the alkylating anthracycline may be administered simultaneously with the

recombinant humanized anti-HER2 antibody, or the compounds may be administered sequentially, in either order.

In the method of the subject invention, for the administration of the alkylating anthracycline of formula Ia or Ib as defined above, the course of therapy generally employed is from about 0.1 to about 200 mg/m^2 of body surface area. More preferably, the course therapy employed is from about 1 to about 50 mg/m^2 of body surface area.

In the method of the subject invention, for the administration of the recombinant humanized anti-HER2 antibody, for example for the administration of the recombinant humanized monoclonal antibody anti-HER2 trastuzumab, the course of therapy generally employed is from about 1 to about 1000 mg/m^2 of body surface area. More preferably, the course therapy employed is from about 50 to about 500 mg/m^2 of body surface area.

The antineoplastic therapy of the present invention is, in particular, suitable for treating breast, ovary, lung, colon, kidney, stomach, pancreas, liver, melanoma, leukemia and brain tumors in mammals, including humans. More in particular, the combined use of an alkylating anthracycline according to the invention and a recombinant humanized anti-HER2 antibody, for example the recombinant humanized monoclonal antibody anti-HER2 trastuzumab, can be suitable for the treatment of patients with cancers over-expressing the HER2 protein, for example, for patient with metastatic breast cancer over-expressing the HER2 protein.

The antineoplastic therapy according to this invention also comprises the prevention and/or treatment of tumor metastasis.

A still further aspect of the present invention is the use of an alkylating anthracycline of formula Ia or Ib as defined above and a recombinant humanized anti-HER2 antibody, preferably the recombinant humanized monoclonal antibody anti-HER2 trastuzumab, for the treatment of tumors by angiogenesis inhibition.

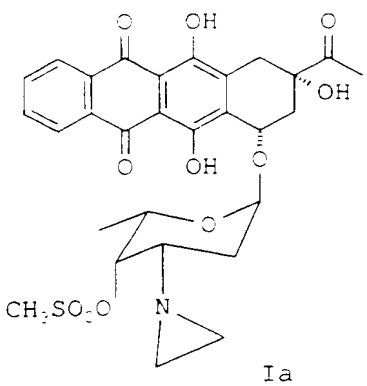
As stated above, the effectiveness of an alkylating anthracycline of formula Ia or Ib and a recombinant humanized anti-HER2 antibody is significantly increased without a parallel increased toxicity. In other words, the combined therapy of the present invention enhances the antitumoral effects of the alkylating anthracycline of formula Ia or Ib as defined above and of a recombinant humanized anti-HER2 antibody and thus yields the most effective and least toxic treatment for tumors.

The synergistic action displayed by the combined preparations according to the present invention can be shown, for instance, by testing the activity of the combination in mice bearing human tumor xenografts overexpressing HER2 protein, following, for example, the method described in Cancer Research, 1998, 58:2825-2831.

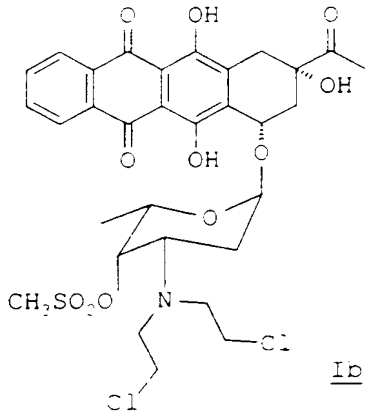
Suitable modifications and adaptations of a variety of conditions and parameters normally encountered in clinical therapy which are obvious to those skilled in the art are within the scope of this invention.

CLAIMS

1. Products containing an alkylating anthracycline of formula Ia or Ib:



Ia



Ib

and a recombinant humanized anti-HER2 antibody as a combined preparation for simultaneous, separate or sequential use in antitumor therapy.

2. Products according to claim 1, wherein the recombinant humanized anti-HER2 antibody is the recombinant humanized monoclonal antibody anti-HER2 trastuzumab.

3. Products according to claim 1 or 2, wherein the alkylating anthracycline is 4-demethoxy-3'-deamino-3'-aziridinyl-4'-methansulfonyl daunorubicin.

4. Products according to any one of claims 1 to 3, wherein the antitumor therapy is for treating cancers over-expressing HER2 protein.

5. A pharmaceutical composition comprising a pharmaceutically acceptable carrier or excipient and, as active ingredient, an alkylating anthracycline of formula Ia or Ib as defined in claim 1 and a recombinant humanized anti-HER2 antibody.

6. A pharmaceutical composition according to claim 5 wherein the recombinant humanized anti-HER2 antibody is the recombinant humanized monoclonal antibody anti-HER2 trastuzumab.

7. Use of an alkylating anthracycline of formula Ia or Ib as defined in claim 1 and a recombinant humanized anti-HER2 antibody in the preparation of a medicament for use in the treatment of tumors, wherein the alkylating anthracycline and the recombinant humanized anti-HER2 antibody are administered simultaneously, separately or sequentially.

8. Use according to claim 7 wherein the recombinant humanized anti-HER2 antibody is the recombinant humanized monoclonal antibody anti-HER2 trastuzumab.

9. Use of an alkylating anthracycline of formula Ia or Ib as defined in claim 1 and a recombinant humanized anti-HER2 antibody in the preparation of a medicament for use in the prevention and/or treatment of tumor metastasis, wherein the alkylating anthracycline and the recombinant humanized anti-HER2 antibody are administered simultaneously, separately or sequentially.

10. Use according to claim 9 wherein the recombinant humanized anti-HER2 antibody is the recombinant humanized monoclonal antibody anti-HER2 trastuzumab.

11. A method of treating a mammal, including a human, suffering from a neoplastic disease comprising administering to said mammal an alkylating anthracycline of formula Ia or Ib as defined above and a recombinant humanized anti-HER2 antibody, in amounts effective to produce a synergistic antineoplastic effect.

12. A method according to claim 11, wherein the recombinant humanized anti-HER2 antibody is the recombinant humanized monoclonal antibody anti-HER2 trastuzumab.

13. A method for lowering the side effects caused by antineoplastic therapy with an antineoplastic agent in a mammal, including a human, in need thereof, the method comprising administering to said mammal a combined preparation comprising an alkylating anthracycline of formula Ia or Ib as defined above, and a recombinant humanized anti-HER2 antibody, in amounts effective to produce a synergistic antineoplastic effect.

14. A method according to claim 13, wherein the recombinant humanized anti-HER2 antibody is the recombinant humanized monoclonal antibody anti-HER2 trastuzumab.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(71) Applicant *(for all designated States except US)*: **PHARMACIA & UPJOHN S.P.A.** [IT/IT]; Via Robert Koch, 1.2, I-20152 Milano (IT).

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(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
-- *Without international search report and to be republished upon receipt of that report.*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 01/05425 A2

(54) Title: COMBINED PREPARATIONS COMPRISING ANTITUMOR AGENTS

(57) Abstract: There are provided the combined use of 4-demethoxy-3'-deamino-3'-aziridinyl-4'-methansulfonyl daunorubicin or 4-demethoxy-N,N-bis(2-chloroethyl)-4'-methansulfonyl daunorubicin and a recombinant humanized anti-HER2 antibody, preferably trastuzumab, in the treatment of tumors and the use of said combination in the treatment and/or prevention of tumor metastasis.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
FC 874/5		

International application No.	International filing date (day/month/year)	Priority date (day/month/year)
PCT/EP00/06540	10/07/2000	20/07/1999

International Patent Classification (IPC) or national classification and IPC
A61K39/00

Applicant
PHARMACIA AND UPJOHN S.P.A. et al.

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 9 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☒ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
24/01/2001	19.10.2001

Name and mailing address of the international preliminary examining authority:

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Herrero, M

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP00/06540

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-5 as originally filed

Claims, No.:

1-14 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 11-14 with respect to industrial applicability.

because:

☒ the said international application, or the said claims Nos. 11-14 relate to the following subject matter which does not require an international preliminary examination (*specify*):
see separate sheet

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-14
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-14
Industrial applicability (IA)	Yes:	Claims	1-10

No: Claims

2. Citations and explanations
see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

SECTION III

Claims 11-14 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT (i.e. methods of treatment of the human or animal body by therapy). Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

SECTION V

2. CITATIONS AND EXPLANATIONS

2.1 The following documents have been considered for the purposes of this report:

D1: Baselga, J. et al (1997) Oncology **11**:43-48
D2: WO 99/31140
D3: Pegram, M. et al (April 1999) Oncogene **18**:2241-2251

The document D3 was not cited in the international search report. A copy of the document has been provided to the applicants.

2.2 Inventive step (Art. 33(3) PCT)

The present application does not satisfy the criterion set forth in Article 33(3) PCT because the subject-matter claimed does not involve an inventive step (Rule 65(1)(2) PCT).

Among other relevant teachings D1 reviews the results (i) of the combined administration of either paclitaxel or doxorubicin (the two chemotherapeutic agents most active against breast cancer) with MoAb 4D5 (a murine anti-human HER2 monoclonal antibody) to mice bearing breast cancer human tumor xenografts expressing high levels of $p185^{HER2}$ (cf page 46, right column, lines 18-44) and (ii) of the administration in a phase II clinical study of rhuMoab HER2

(seemingly the same recombinant humanized monoclonal antibody identified in the present application as trastuzumab Herceptin™) in combination with cisplatin to patients with breast carcinomas that overexpress p185 ^{HER2} and a history of proven refractoriness to chemotherapy. The results of said combined therapy in these patients suggested that the synergy observed in the laboratory was reproducible in the clinic (cf paragraph bridging pages 46-47). Furthermore, D1 also reports the ongoing phase III multinational study of chemotherapy, i.e. either cyclophosphamide and doxorubicin (or epirubicin) or paclitaxel, in combination with rhuMoab HER-2 in patients with HER2-overexpressing breast tumors who had not received prior chemotherapy for metastatic disease (cf page 47, left column and Figure 2).

D2 relates to the treatment of human patients susceptible to or diagnosed with cancer overexpressing ErbB2 (also known as HER2) with a combination of an anti-ErB2 humanized antibody (e.g. the HERCEPTIN™) and a chemotherapeutic agent other than an anthracycline, e.g. doxorubicin or epirubicin. The experimental data provided in D2 (cf Example on pages 27-30) substantiate that the combination of anti-ErbB2 antibody treatment with chemotherapy markedly increases the clinical benefit as assessed by response dates and the evaluation of disease progression. However, due to the increased cardiac side-effects of doxorubicin or epirubicin, the combined use of anthracyclines with anti-ErbB2 antibody therapy is contraindicated (cf last paragraph on page 30). It would appear that the technical information provided in the experimental section of D2 corresponds to the results of the ongoing phase III clinical trial referred to in D1 (see above).

D3 studies the inhibitory effects of combinations of HER-2/neu antibody and chemotherapeutic agents used for treatment of human breast cancers both *in vitro* and *in vivo*. Attention is drawn to the paragraph bridging pages 2249-2250 concerning the method therein carried out for the analysis of rhuMab HER-2 in combination with cytotoxic chemotherapeutic drugs (i.e. doxorubicin, methotrexate, etopoxide, 5-fluorouracil, vinblastin, cyclophosphamide and paclitaxel) against HER-2/neu-overexpressing breast carcinoma xenografts *in vivo*

The present application describes and claims combined preparations comprising two types of antitumor agents, i.e. a daunorubicin (an alkylating anthracycline) and a recombinant humanized anti-HER2 antibody, and their therapeutic uses, especially for treating cancers over-expressing HER2 protein.

According to the description "*The effectiveness of an alkylating anthracycline of formula Ia or Ib* (i.e. the daunorubicin compound) *and a recombinant humanized anti-HER2 antibody is significantly increased without a parallel increased toxicity. In other words, the combined therapy of the present invention enhances the antitumoral effects of the alkylating anthracycline of formula Ia or Ib and of a recombinant humanized anti-HER2 antibody and thus yields the most effective and least toxic treatment for tumors*" (cf page 5, lines 1-9).

In spite of the foregoing statements no experimental support can be found elsewhere in the description as originally filed showing that the expected technical effects, i.e. *in vivo* antineoplastic synergism not associated with an increased toxicity in human patients, are obtained.

The invitation found on page 5, lines 10-15 to carry out conventional *in vivo* assays in mice bearing human tumor xenografts overexpressing HER2 protein (of the type disclosed in D1 or D3, see above) with the intended compositions described in the present application cannot substantiate the presence of an inventive step associated with the subject-matter hereby claimed, contrary to Art. 33(3) PCT, all the more when considering the aforementioned results obtained in the phase III clinical trial reported in D2 with respect to the undesirable effects of a corresponding treatment involving the combined administration of HERCEPTIN™ with anthracycline compounds as doxorubicin.

Attention is drawn to the fact that both daunorubicin and doxorubicin are anthracycline antibiotic compounds which basically share the same mode of action (i.e. according to D2, page 12, lines 4-5 both are topo II inhibitors) and therefore, in the absence of suitable evidence of a technical nature demonstrating the contrary, a similar undesirable cardiac side-effect as the one referred to in D2 could in principle be expected for both of them, when used in combined treatments equivalent to those intended in present Claims 11-14.

Consequently, the application fails to contain the necessary technical information on the basis of which it could be possible to assess whether the various aspects of the alleged invention as defined in Claims 1-4, 5-6 and 7-10 (products for medical uses, pharmaceutical compositions, second medical indication manufacture formats) or Claims 11-14 (therapeutic methods) involve an inventive step over the teachings derivable from the related prior art (in particular D2), contrary to the requirements of Art. 33(3) PCT.

2.3 Industrial applicability (Art. 33(4) PCT)

For the assessment of the present Claims 1-5, 7-10 and 11-14 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

2.4 In addition to the foregoing, the earlier document WO 00/69460 cited in the International Search Report is brought to the Applicant's attention in view of the provisions of Article 54(3)(4) EPC.

SECTION VII

Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the documents D1, D2 and D3 is not mentioned in the description, nor are these documents identified therein.

SECTION VIII

1. Independent Claims 1 and 13 do not meet the requirements of Article 6 PCT in that the matter for which protection is sought is not clearly defined. These claims

attempt to define the intended therapeutic methods in terms of the result to be achieved which merely amounts to a statement of the underlying problem. The technical features necessary for achieving this result, i.e. the actual amounts effective to produce the pursued synergistic antineoplastic effect, should have been added.

2. The statement in the description on page 5, last paragraph, implies that the subject-matter for which protection is sought may be different to that defined by the claims, thereby resulting in lack of clarity (Article 6 PCT) when used to interpret them (see also the PCT Guidelines, III-4.3a).

INTERNATIONAL SEARCH REPORT

Interna[illegible]al Application No
PCT/EP 00/06540

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/70 A61K39/395 A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, MEDLINE, BIOSIS, CHEM ABS Data, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	BASELGA J ET AL: "HER2 Overexpression and Paclitaxel sensitivity in breast cancer: Therapeutic implications" ONCOLOGY,CH,S. KARGER AG, BASEL, vol. 11, no. 3, SUPPL. 02, March 1997 (1997-03), pages 43-48, XP002100077 ISSN: 0030-2414 abstract page 46, column 2, paragraph 4 -page 47, column 1 ---	1-14
Y	US 5 677 171 A (SHEPARD H MICHAEL ET AL) 14 October 1997 (1997-10-14) claims 18,19,37,39 ---	1-14
	-/--	

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
20 December 2000	29/12/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Gonzalez Ramon, N

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INTERNATIONAL SEARCH REPORT

Intern ial Application No
PCT/EP 00/06540

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5 705 157 A (GREENE MARK I) 6 January 1998 (1998-01-06) claims 2,5	1-14
E	WO 00 69460 A (GENENTECH INC) 23 November 2000 (2000-11-23) abstract page 11, line 20-23; claims 2,3,7	1-14
X	WO 99 31140 A (GENENTECH INC) 24 June 1999 (1999-06-24) page 12, line 4-6; claims 1,4 abstract	1-14
E	WO 00 44225 A (DANNENBERG ANDREW J ;CORNELL RES FOUNDATION INC (US); SUBBARAMAIAH) 3 August 2000 (2000-08-03) page 21 -page 22; claims 2,3,5	1-14
E	WO 00 61185 A (BELLET ROBERT E ;VOGEL CHARLES L (US)) 19 October 2000 (2000-10-19) claims 1,3	1-14
Y	WO 89 06692 A (GENENTECH INC) 27 July 1989 (1989-07-27) page 11, line 12-25; claims 23,28,32 page 12, line 33-35	1-14
Y	EP 0 328 147 A (BRISTOL MYERS CO) 16 August 1989 (1989-08-16) page 8 -page 9; claims 5,11-13,24,26	1-14

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

Interr. ...al Application No
PCT/EP 00/06540

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5677171 A	14-10-1997	US 5772997 A	30-06-1998
		US 5770195 A	23-06-1998
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		US 5122368 A	16-06-1992
		ZA 8900938 A	29-11-1989

INTERNATIONAL SEARCH REPORT

Intern ial Application No
PCT/EP 00/06540

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5 705 157 A (GREENE MARK I) 6 January 1998 (1998-01-06) claims 2,5	1-14
E	WO 00 69460 A (GENENTECH INC) 23 November 2000 (2000-11-23) abstract page 11, line 20-23; claims 2,3,7	1-14
X	WO 99 31140 A (GENENTECH INC) 24 June 1999 (1999-06-24) page 12, line 4-6; claims 1,4 abstract	1-14
E	WO 00 44225 A (DANNENBERG ANDREW J ;CORNELL RES FOUNDATION INC (US); SUBBARAMAIAH) 3 August 2000 (2000-08-03) page 21 -page 22; claims 2,3,5	1-14
E	WO 00 61185 A (BELLET ROBERT E ;VOGEL CHARLES L (US)) 19 October 2000 (2000-10-19) claims 1,3	1-14
Y	WO 89 06692 A (GENENTECH INC) 27 July 1989 (1989-07-27) page 11, line 12-25; claims 23,28,32 page 12, line 33-35	1-14
Y	EP 0 328 147 A (BRISTOL MYERS CO) 16 August 1989 (1989-08-16) page 8 -page 9; claims 5,11-13,24,26	1-14

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PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION CONCERNING SUBMISSION OR TRANSMITTAL OF PRIORITY DOCUMENT

(PCT Administrative Instructions, Section 411)

To:

PHARMACIA & UPJOHN S.P.A.
Patent Department
Viale Pasteur, 10
I-20014 Nerviano
ITALIE

Date of mailing (day month year) 18 September 2000 (18.09.00)	
Applicant's or agent's file reference FC 874 5	**IMPORTANT NOTIFICATION**
International application No. PCT/EP00/06540	International filing date (day month year) 10 July 2000 (10.07.00)
International publication date (day month year) Not yet published	Priority date (day month year) 20 July 1999 (20.07.99)
Applicant PHARMACIA & UPJOHN S.P.A. et al	

1. The applicant is hereby notified of the date of receipt (except where the letters "NR" appear in the right-hand column) by the International Bureau of the priority document(s) relating to the earlier application(s) indicated below. Unless otherwise indicated by an asterisk appearing next to a date of receipt, or by the letters "NR", in the right-hand column, the priority document concerned was submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b).

2. This updates and replaces any previously issued notification concerning submission or transmittal of priority documents.

3. An **asterisk(*)** appearing next to a date of receipt, in the right-hand column, denotes a priority document submitted or transmitted to the International Bureau but not in compliance with Rule 17.1(a) or (b). In such a case, **the attention of the applicant is directed** to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

4. The **letters "NR"** appearing in the right-hand column denote a priority document which was not received by the International Bureau or which the applicant did not request the receiving Office to prepare and transmit to the International Bureau, as provided by Rule 17.1(a) or (b), respectively. In such a case, **the attention of the applicant is directed** to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

Priority date	Priority application No.	Country or regional Office or PCT receiving Office	Date of receipt of priority document
20 July 1999 (20.07.99)	9917012.8	GB	10 Augu 2000 (10.08.00)

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 740.14.35

Authorized officer

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PATENT COOPERATION TREATY

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I-20014 Nerviano
ITALIE

NOTICE INFORMING THE APPLICANT OF THE COMMUNICATION OF THE INTERNATIONAL APPLICATION TO THE DESIGNATED OFFICES

(PCT Rule 47.1(c), first sentence)

Date of mailing (day, month, year) 25 January 2001 (25.01.01)	
Applicant's or agent's file reference FC 8745	**IMPORTANT NOTICE**

International application No.	**International filing date** (day, month, year)	**Priority date** (day, month, year)
PCT/EP00/06540	10 July 2000 (10.07.00)	20 July 1999 (20.07.99)

Applicant
PHARMACIA & UPJOHN S.P.A. et al

1. Notice is hereby given that the International Bureau has communicated, as provided in Article 20, the international application to the following designated Offices on the date indicated above as the date of mailing of this Notice:
   AU,KP,KR,US

   In accordance with Rule 47.1(c), third sentence, those Offices will accept the present Notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s).

2. The following designated Offices have waived the requirement for such a communication at this time:
   AE,AG,AL,AM,AP,AT,AZ,BA,BB,BG,BR,BY,BZ,CA,CH,CN,CR,CU,CZ,DE,DK,DM,DZ,EA,EE,EP,ES, FI,GB,GD,GE,GH,GM,HR,HU,ID,IL,IN,IS,JP,KE,KG,KZ,LC,LK,LR,LS,LT,LU,LV,MA,MD,MG,MK, MN,MW,MX,MZ,NO,NZ,OA,PL,PT,RO,RU,SD,SE,SG,SI,SK,SL,TJ,TM,TR,TT,TZ,UA,UG,UZ,VN,YU,
   The communication will be made to those Offices only upon their request. Furthermore, those Offices do not require the applicant to furnish a copy of the international application (Rule 49.1(a-bis)).

3. Enclosed with this Notice is a copy of the international application as published by the International Bureau on
   25 January 2001 (25.01.01) under No. WO 01/05425

REMINDER REGARDING CHAPTER II (Article 31(2)(a) and Rule 54.2)

If the applicant wishes to postpone entry into the national phase until 30 months (or later in some Offices) from the priority date, **a demand for international preliminary examination** must be filed with the competent International Preliminary Examining Authority before the expiration of 19 months from the priority date.

It is the applicant's sole responsibility to monitor the 19-month time limit.

Note that only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination.

REMINDER REGARDING ENTRY INTO THE NATIONAL PHASE (Article 22 or 39(1))

If the applicant wishes to proceed with the international application in the **national phase**, he must, within 20 months or 30 months (or later in some Offices), perform the acts referred to therein before each designated or elected Office.

For further important information on the time limits and acts to be performed for entering the national phase, see the Annex to Form PCT/IB/301 (Notification of Receipt of Record Copy) and Volume II of the PCT Applicant's Guide.

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. 41-22/740.14.35

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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
FC 874/5		
International application No.	International filing date (day/month/year)	Priority date (day/month/year)
PCT/EP00/06540	10/07/2000	20/07/1999
International Patent Classification (IPC) or national classification and IPC A61K39/00		
Applicant PHARMACIA AND UPJOHN S.P.A. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 9 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☒ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
24/01/2001	9.8.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Herrero, M. Telephone No.: +49 89 2399 8542

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP00/06540

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-5 as originally filed

Claims, No.:

1-14 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 11-14 with respect to industrial applicability.

because:

☒ the said international application, or the said claims Nos. 11-14 relate to the following subject matter which does not require an international preliminary examination (*specify*):
see separate sheet

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-14
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-14
Industrial applicability (IA)	Yes:	Claims	1-10

No: Claims

2. Citations and explanations
see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

SECTION III

Claims 11-14 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT (i.e. methods of treatment of the human or animal body by therapy). Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

SECTION V

2. CITATIONS AND EXPLANATIONS

2.1 The following documents have been considered for the purposes of this report:

D1: Baselga, J. et al (1997) Oncology **11**:43-48
D2: WO 99/31140
D3: Pegram, M. et al (April 1999) Oncogene **18**:2241-2251

The document D3 was not cited in the international search report. A copy of the document has been provided to the applicants.

2.2 Inventive step (Art. 33(3) PCT)

The present application does not satisfy the criterion set forth in Article 33(3) PCT because the subject-matter claimed does not involve an inventive step (Rule 65(1)(2) PCT).

Among other relevant teachings D1 reviews the results (i) of the combined administration of either paclitaxel or doxorubicin (the two chemotherapeutic agents most active against breast cancer) with MoAb 4D5 (a murine anti-human HER2 monoclonal antibody) to mice bearing breast cancer human tumor xenografts expressing high levels of $p185^{HER2}$ (cf page 46, right column, lines 18-44) and (ii) of the administration in a phase II clinical study of rhuMoab HER2

(seemingly the same recombinant humanized monoclonal antibody identified in the present application as trastuzumab Herceptin™) in combination with cisplatin to patients with breast carcinomas that overexpress p185 ^{HER2} and a history of proven refractoriness to chemotherapy. The results of said combined therapy in these patients suggested that the synergy observed in the laboratory was reproducible in the clinic (cf paragraph bridging pages 46-47). Furthermore, D1 also reports the ongoing phase III multinational study of chemotherapy, i.e. either cyclophosphamide and doxorubicin (or epirubicin) or paclitaxel, in combination with rhuMoab HER-2 in patients with HER2-overexpressing breast tumors who had not received prior chemotherapy for metastatic disease (cf page 47, left column and Figure 2).

D2 relates to the treatment of human patients susceptible to or diagnosed with cancer overexpressing ErbB2 (also known as HER2) with a combination of an anti-ErB2 humanized antibody (e.g. the HERCEPTIN™) and a chemotherapeutic agent other than an anthracycline, e.g. doxorubicin or epirubicin. The experimental data provided in D2 (cf Example on pages 27-30) substantiate that the combination of anti-ErbB2 antibody treatment with chemotherapy markedly increases the clinical benefit as assessed by response dates and the evaluation of disease progression. However, due to the increased cardiac side-effects of doxorubicin or epirubicin, the combined use of anthracyclines with anti-ErbB2 antibody therapy is contraindicated (cf last paragraph on page 30). It would appear that the technical information provided in the experimental section of D2 corresponds to the results of the ongoing phase III clinical trial referred to in D1 (see above).

D3 studies the inhibitory effects of combinations of HER-2/neu antibody and chemotherapeutic agents used for treatment of human breast cancers both *in vitro* and *in vivo*. Attention is drawn to the paragraph bridging pages 2249-2250 concerning the method therein carried out for the analysis of rhuMab HER-2 in combination with cytotoxic chemotherapeutic drugs (i.e. doxorubicin, methotrexate, etopoxide, 5-fluorouracil, vinblastin, cyclophosphamide and paclitaxel) against HER-2/neu-overexpressing breast carcinoma xenografts *in vivo*

The present application describes and claims combined preparations comprising two types of antitumor agents, i.e. a daunorubicin (an alkylating anthracycline) and a recombinant humanized anti-HER2 antibody, and their therapeutic uses, especially for treating cancers over-expressing HER2 protein.

According to the description "*The effectiveness of an alkylating anthracycline of formula Ia or Ib* (i.e. the daunorubicin compound) *and a recombinant humanized anti-HER2 antibody is significantly increased without a parallel increased toxicity. In other words, the combined therapy of the present invention enhances the antitumoral effects of the alkylating anthracycline of formula Ia or Ib and of a recombinant humanized anti-HER2 antibody and thus yields the most effective and least toxic treatment for tumors*" (cf page 5, lines 1-9).

In spite of the foregoing statements no experimental support can be found elsewhere in the description as originally filed showing that the expected technical effects, i.e. *in vivo* antineoplastic synergism not associated with an increased toxicity in human patients, are obtained.

The invitation found on page 5, lines 10-15 to carry out conventional *in vivo* assays in mice bearing human tumor xenografts overexpressing HER2 protein (of the type disclosed in D1 or D3, see above) with the intended compositions described in the present application cannot substantiate the presence of an inventive step associated with the subject-matter hereby claimed, contrary to Art. 33(3) PCT, all the more when considering the aforementioned results obtained in the phase III clinical trial reported in D2 with respect to the undesirable effects of a corresponding treatment involving the combined administration of HERCEPTIN™ with anthracycline compounds as doxorubicin.

Attention is drawn to the fact that both daunorubicin and doxorubicin are anthracycline antibiotic compounds which basically share the same mode of action (i.e. according to D2, page 12, lines 4-5 both are topo II inhibitors) and therefore, in the absence of suitable evidence of a technical nature demonstrating the contrary, a similar undesirable cardiac side-effect as the one referred to in D2 could in principle be expected for both of them, when used in combined treatments equivalent to those intended in present Claims 11-14.

Consequently, the application fails to contain the necessary technical information on the basis of which it could be possible to assess whether the various aspects of the alleged invention as defined in Claims 1-4, 5-6 and 7-10 (products for medical uses, pharmaceutical compositions, second medical indication manufacture formats) or Claims 11-14 (therapeutic methods) involve an inventive step over the teachings derivable from the related prior art (in particular D2), contrary to the requirements of Art. 33(3) PCT.

2.3 Industrial applicability (Art. 33(4) PCT)

For the assessment of the present Claims 1-5, 7-10 and 11-14 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

2.4 In addition to the foregoing, the earlier document WO 00/69460 cited in the International Search Report is brought to the Applicant's attention in view of the provisions of Article 54(3)(4) EPC.

SECTION VII

Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the documents D1, D2 and D3 is not mentioned in the description, nor are these documents identified therein.

SECTION VIII

1. Independent Claims 1 and 13 do not meet the requirements of Article 6 PCT in that the matter for which protection is sought is not clearly defined. These claims

attempt to define the intended therapeutic methods in terms of the result to be achieved which merely amounts to a statement of the underlying problem. The technical features necessary for achieving this result, i.e. the actual amounts effective to produce the pursued synergistic antineoplastic effect, should have been added.

2. The statement in the description on page 5, last paragraph, implies that the subject-matter for which protection is sought may be different to that defined by the claims, thereby resulting in lack of clarity (Article 6 PCT) when used to interpret them (see also the PCT Guidelines, III-4.3a).